

On cake

There are times when the only thing that keeps us going is the thought of cake with coffee. It is something to look forward to, a soupçon of joy linking us to lunch, which can often seem a long time away when you are sitting in front of a blank computer screen with a blanker brain.

Cake, however, is often not available. The reasons are many and varied, but cake is not part of anybody's healthy living checklist. The things that really matter, like exercise, sensible diets and drinking, and so on. Bandolier has commented before that keeping healthy makes a huge difference, and a new report of an ongoing observational study from Hawaii emphasises the point. Nor is it too late! Avoiding risk factors for a man of 55 has major impact on being alive, and especially being alive and healthy, at 80 or 85. That's lots more time for cake.

Controversy is a useful substitute when cake is not available. A bit of controversy can make the blood flow a bit faster. So a few controversies - all of which come down to the nature of the evidence that people have chosen to use or ignore. In asthma, several meta-analyses come to different conclusions over long-acting beta-agonists added to inhaled corticosteroids. Trouble is, included studies in some meta-analyses didn't have the inhaled corticosteroids in the first place, which makes interpretation a tad difficult, and perhaps an interpretation too far.

Guidelines never get tested. They may give us a nice fluffy feeling inside, but a guideline that isn't tested is a waste of time and space. Too often when they are looked at, either the evidence is poor, or people just don't follow them. Either way, it isn't good management.

Next month Bandolier has another birthday. Birthdays are Nature's way of telling us to eat more cake. And birthdays are good for us, because people with the most live the longest.

In this issue

SMBG and glycaemic control.....	p. 1
NSAIDs, gastroprotection, and guidelines	p. 3
Long-acting beta-agonist controversy	p. 4
Selenium and CHD.....	p. 5
Healthy survival	p. 6
Antibiotics for acute otitis externa	p. 7
Antibiotics for acute otitis media	p. 8

SMBG AND GLYCAEMIC CONTROL

Bandolier is always on the lookout for useful papers on self monitoring of blood glucose, especially in those with type-2 diabetes. The ongoing controversy makes it interesting. A small number of small, inadequate, randomised trials say that self monitoring is not useful, yet this, and a few small observational studies hold sway over large, good, observational studies that point to substantial benefits. One such study in Germany featured in Bandolier 147.

We now have another large and impressive observational study with some unique features [1]. The results support common sense and experience over inadequate assessment of evidence - another fine example about why we need good evidence assessment.

Study

The study was designed to examine the association between changes in SMBG frequency and glycaemic control over four years. Two large cohorts were used to do this, identified from a diabetes registry with about 180,000 patients, part of a larger group of three million patients. Eligibility included members with continuous membership and full pharmacy benefits to avoid obvious problems if neither condition were met.

The first cohort had 16,000 patients who were not practising self monitoring of blood glucose at baseline. The longitudinal changes in HbA_{1c} were evaluated over four years, according to those who became users, and those who were persistent non-users.

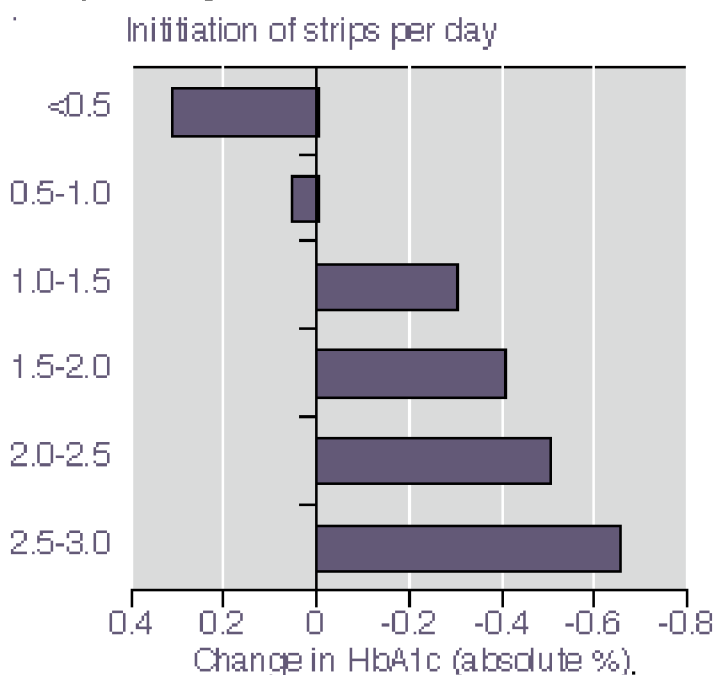
The second cohort was 15,000 prevalent users who were practising self monitoring at baseline. This assessed how individual changes in frequency of self monitoring were reflected in HbA_{1c} over three years.

Patients were classified as being on no medication, oral hypoglycaemic agents, or insulin. Patients switching between therapies were excluded, so groups refer to those who were on that treatment only for the period of observation, though dose changes within a type of therapy could have occurred.

Results

The average age of patients in various groups was 53 to 67 years, with insulin users tending to be younger, and less likely to be female. Average initial HbA_{1c} concentrations also differed between groups. Changes in HbA_{1c} concentrations

Figure 1: Association between change in strip use and change in HbA1c concentration over four years in patients on no medication



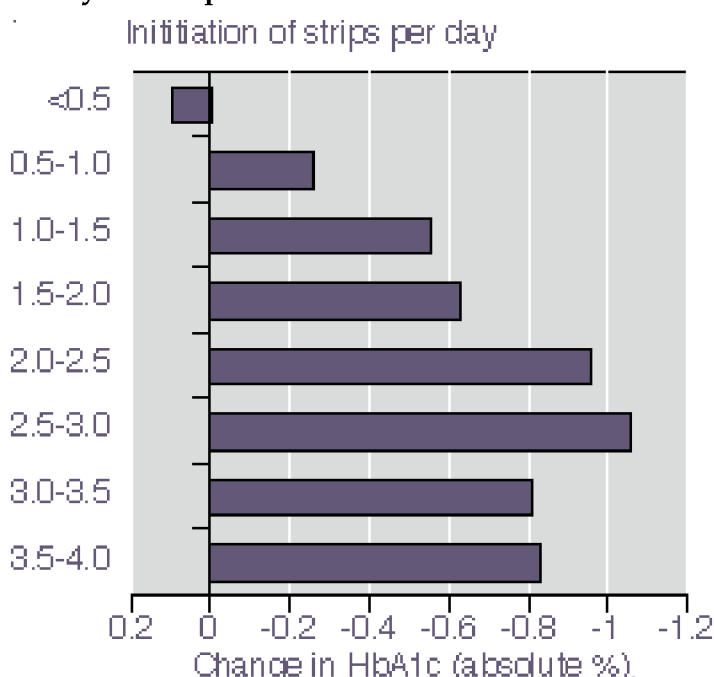
were adjusted for age, sex, comorbidity, baseline HbA_{1c} concentration, and a number of other relevant factors.

New users of SMBG

For those on no medication, new users had higher initial HbA_{1c} concentrations (8.2%) than persistent nonusers (6.6%). In the 7,800 new users, HbA_{1c} concentrations fell by larger amounts according to the number of strips per day used (Figure 1).

For those on oral hypoglycaemics only, new users had higher initial HbA_{1c} concentrations (8.6%) than persistent nonusers

Figure 1: Association between change in strip use and change in HbA1c concentration over four years in patients on no medication



(7.3%). In the 5,500 new users, HbA_{1c} concentrations fell by larger amounts according to the number of strips per day used (Figure 2), up to three strips per day.

Insulin users had high HbA_{1c} concentrations (9.3%), and in 840 of them there was a similar greater decrease in HbA_{1c} concentration with increasing strip use, by a maximum of about 0.8% with three strips per day or more.

Prevalent users of SMBG

In the prevalent cohort, those on no medication had the lowest HbA_{1c} concentration (6.4%), those on oral hypoglycaemic drugs only a higher HbA_{1c} concentration (7.6%), and those on insulin only the highest (8.1%). The average absolute change in frequency of strip use was 0.4, 0.5, and 1.1 strips per day respectively.

Among 1,600 patients on no medication, changes in strip frequency were not associated with change in HbA_{1c} concentrations. In those on oral hypoglycaemic drugs only (7,400) or insulin only (6,300), subsequent increases in strip use by one strip daily resulted in 0.16% and 0.12% reduction in HbA_{1c} concentrations respectively. There was a dose response for increasing use of strips.

Comment

These results are absolutely in line with what we have come to expect from large, good, observational studies related to self monitoring of blood glucose and glycaemic control as measured by HbA_{1c} concentrations. It says that increased use results in better glycaemic control, and (if you look at the data), that you get better results with those with a higher initial HbA_{1c} concentration. Common, sense, really.

Bandolier likes the advice on SMBG in type 2 diabetes given by an international committee in 2005 [2]. It said that individuals offered self monitoring of blood glucose on an ongoing basis might include recently diagnosed diabetics, those with more erratic lifestyles, people with problems with hypoglycaemia, and those keen to tighten their glucose control, which is what doctors and other professionals are very good at doing.

That seems more sensible than a blanket view of cost effectiveness based on flawed evidence, which is what we seem have in the UK. To recap, much weight has previously been given to a meta-analysis of tiny, invalid, randomised trials, and some small observational studies. Less weight seems to have been given to large, well-conducted, observational studies. It is a bit more complicated, but even a passing knowledge of diabetes combined with an appreciation of what constitutes good evidence leads to the obvious conclusion that SMBG is worthwhile in some patients.

References:

- 1 AJ Karter et al. Longitudinal study of new and prevalent use of self-monitoring of blood glucose. *Diabetes Care* 2006 29: 1757-1763.
- 2 Global guidelines for type 2 diabetes. International Diabetes Federation, 2005 (www.idf.org).

GASTROPROTECTION WITH NSAID:

DO WE FOLLOW GUIDELINES?

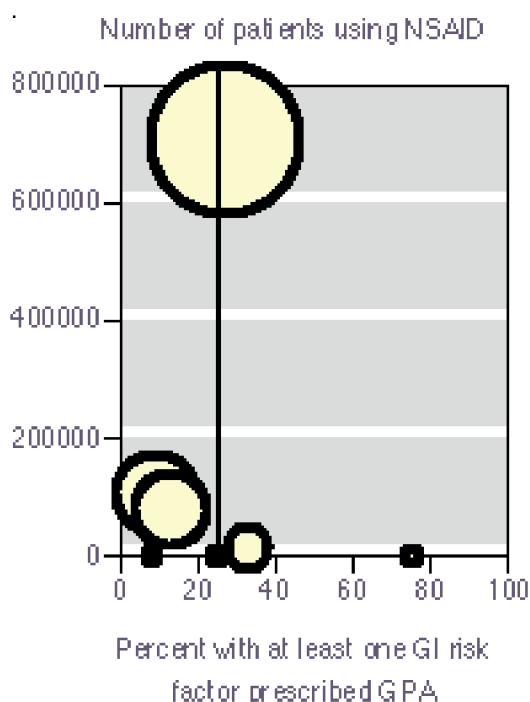
Current UK clinical guidance on NSAID use suggests a number of factors that put patients at higher risk of an NSAID-induced gastrointestinal adverse event. These include age over 65 years, previous history, comorbidity, prolonged use, high doses, and other drugs, like aspirin or anticoagulants. If people have at least one of these risk factors, and have to take an NSAID, it is recommended that they be prescribed some form of gastroprotection, principally a proton pump inhibitor (PPI) or higher dose histamine antagonist (H2A). Similar guidance exists in other parts of the world.

The effectiveness of any strategy is the product of efficacy in clinical trials, and the usability of the strategy in clinical practice. For drugs, this means that prescribing of a medicine is appropriate, and that patients prescribed the medicine take it. Medicines not taken cannot be effective. A new systematic review [1] suggests that, in this area at least, guidance is hardly ever followed by action.

Systematic review

As part of a wider review, it sought evidence concerning levels of prescribing of gastroprotective strategies with non-selective NSAIDs to patients with one or more risk factors for gastrointestinal bleeding, and whether prescribing was described as appropriate against any prescribing guidance. It also looked for evidence concerning adherence to prescribed gastroprotective strategies with non-selective NSAIDs. Searching was up to the end of 2005.

Figure 1: Individual studies reporting patients with at least one GI risk factor prescribed gastroprotective regimen. Vertical line is average, and size of symbol is proportional to size of study



Results

The review found 11 studies relating appropriateness of use of gastroprotective strategies in patients using NSAIDs and published since 2002. These studies included 1.56 million patients, of whom 911,000 were recipients of NSAIDs. Eight of the 11 studies reported that large proportions of patients with gastrointestinal risk factors (including age ≥ 65 years) were not receiving appropriate gastroprotection.

In what appeared to be mainly primary care populations, non-use of gastroprotection in patients with at least one gastrointestinal risk factor was about 73% to 90% in the USA, 76% in Italy, 87% in Holland, 65% in Canada, and 76% in the UK. A study in secondary care in the UK found no gastroprotection in 76% of patients with at least one gastrointestinal risk factor, but gastroprotection non-use was lower at 25% in a cohort of patients following a diagnosed ulcer or bleed. Pooling these 11 studies (Figure 1), 76% (3 out of 4) of the patients with at least one gastrointestinal risk factor did not receive a prescription for a gastroprotective agent.

Comment

Many NSAID users have a risk factor for NSAID-associated gastrointestinal problems, even if it is only age. Typically, studies find that about half of typical NSAID users should be prescribed a protective agent like a PPI or H2A with NSAID. The evidence is that guidance that suggests use of gastroprotective agents with NSAIDs where there is at least one risk factor is not followed.

Nor has the picture changed since 2005. One large (11,500 patients, mainly with rheumatoid arthritis) survey [2] concluded that use of gastroprotection was similar in patients taking NSAIDs, coxibs, or neither, and was low (35%-40%) even in patients with four different gastrointestinal risk factors. Another also reported a low use of NSAID together with gastroprotective drug in people aged over 65 years, and by definition with at least one risk factor [3].

Together with limited evidence that patients prescribed gastroprotection frequently do not take it, this evidence questions a strategy that has consistently been shown not to work. It is one thing to come up with a guideline: it is quite another to make sure that it is followed. We should do more testing of guidelines.

References:

- 1 RA Moore et al. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 selective inhibitors (coxibs) and gastrointestinal harm: review of clinical trials and clinical practice. *BMC Musculoskeletal Disorders* 2006 7:79 (www.biomedcentral.com/1471-2474/7/79).
- 2 EB Garcia et al. Gastrointestinal prophylactic therapy among patients with arthritis treated by rheumatology specialists. *Journal of Rheumatology* 2006 33:779-784.
- 3 MA Steinman et al. Age and rising rates of cyclooxygenase-2 inhibitor use. Results from a national survey. *Journal of General Internal Medicine* 2006 21:245-250.

LONG-ACTING BETA-AGONIST CONTROVERSY

Bandolier is usually on the look out for controversy, and examples of where the principles of evidence are misused. Where both circumstances come together, then it is likely that we have a good learning example. Such an occurrence is with conflicting views about what systematic reviews and meta-analyses say about the safety of long acting beta-agonist inhalers taken with inhaled corticosteroids for asthma.

The problem

The problem is neatly outlined by some folk from the Canadian Asthma Guidelines Group [1]. They point out that a meta-analysis published in 2006 [2] has been prominent in questioning the safety of long-acting beta-agonists in asthma. The meta-analysis suggested an increase in severe exacerbations requiring hospital admission, and life-threatening exacerbations requiring intubation and ventilation, with risks of both about doubled.

The problem was that in a large proportion of the studies in this meta-analysis, patients were not required to take inhaled corticosteroids. Yet current guidance endorses long-acting beta-agonists as add-on therapy to inhaled corticosteroids.

The results of this meta-analysis differ from two others, both Cochrane reviews [3,4]. In one, the control for long-acting beta-agonists in addition to inhaled corticosteroid was placebo [3]. In the other, long-acting beta-agonists in addition to inhaled corticosteroid was compared with a higher dose of inhaled corticosteroid [4].

The results of all three meta-analyses for hospital admissions for exacerbations of asthma are shown in Table 1. As well as having different controls for long-acting beta-agonists in addition to inhaled corticosteroid, the total number of events was low in each case, and the event rates generally below 2%.

Comment

With rare but serious adverse events the major difficulty is one of numbers. We often have only small numbers of events. When this is compounded by different comparators,

and especially by comparators that are outside usual treatment guidelines, interpretation becomes especially difficult. A third complication here is that of ethnicity. A large randomised trial designed to look at rare adverse events with long-acting beta-agonists (not necessarily as add-on therapy to inhaled corticosteroids) was originally designed to enrol 60,000 patients, but was discontinued early because of an unexpected deaths in African-American patients [5]. The major effect was in African-Americans not using inhaled corticosteroids.

Increased use of long-acting beta-agonists has occurred at the same time as asthma hospital admissions and mortality have been falling. When patients with asthma are not well controlled with low dose inhaled corticosteroids the options are higher doses of steroids (which has its own drawbacks like cataract and fracture), or long-acting beta-agonists in addition to inhaled corticosteroid.

Benefit and possible harm have to be balanced, something not easily compressed into a headline because the issues are complex [6]. In this case, the lesson seems to be to keep taking the guidance.

Reference:

- 1 P Ernst et al. Safety and effectiveness of long acting inhaled β -agonist bronchodilators when taken with inhaled corticosteroids. *Annals of Internal Medicine* 2006 145:692-694.
- 2 SR Salpeter et al. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Annals of Internal Medicine* 2006 144:904-912.
- 3 M Ni Chroinin et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane database of Systematic Reviews* 2005:CD005535.
- 4 IR Greenstone et al. Combination of long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane database of Systematic Reviews* 2005:CD005533.
- 5 HS Nelson et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006 129:15-26.
- 6 HS Nelson. Long-acting beta-agonists in adult asthma: evidence that these drugs are safe. *Primary Care Respiratory Journal* 2006 15:271-277.

Table 1: Summary of evidence on hospital admissions for asthma from three systematic reviews and meta-analyses that used different standards for inhaled corticosteroids with long-acting beta-agonists

Reference	Inhaled corticosteroids	Trials	Long-acting β -agonists		Control		Odds ratio (95%CI)
			Events/total	Events per 1000	Events/total	Events per 1000	
Salpeter et al, 2006 [1]	Inconsistent use	12	53/3083	17	12/2008	6	2.6 (1.6 to 4.3)
Ni Chroinin et al, 2005 [2]	Same dose both groups	10	26/2097	12	32/2065	16	0.8 (0.5 to 1.4)
Greenstone et al, 2005 [3]	Higher dose in controls	13	12/2470	5	15/2207	7	0.7 (0.3 to 1.5)

SELENIUM AND CHD

The apparently conflicting evidence about whether selenium is protective against heart disease has long intrigued Bandolier. There is something of a rational choice, in that it is involved in protection against oxidative damage. Foods that tend to be selenium rich include plants, meats and seafood, though the content varies with geography and use of fertiliser with selenium. Many people supplement their diets with selenium, often as yeast grown on selenium rich nutrients, often with 100 µg per day or so.

The question is whether such supplementation is helpful, and, indeed, whether selenium levels in the body have any relationship to actual outcomes, like coronary heart disease. A new systematic review and meta-analysis [1] pulls the evidence together, and poses some interesting if difficult questions.

Systematic review

The search examined MEDLINE and Cochrane up to March 2006 for studies that might be relevant. Importantly, it also did some extensive searching of references, which is often as good a source for observational studies as electronic searching. The aim was to identify observational studies assessing the association of selenium content of blood or other tissues with clinical coronary heart disease, as well as any randomised studies examining selenium supplementation.

The main results are shown in Table 1. Cohort studies found a bare statistical association between selenium levels and heart disease, though only one individual cohort study out of 14 individually reached statistical significance. Almost all of these (13/14) had adjusted for confounders like age, sex, smoking, BMI, and other factors.

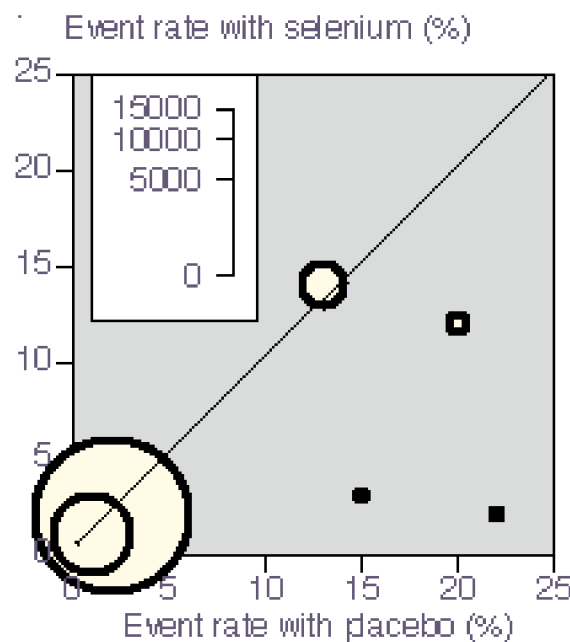
By contrast, case control studies showed a large reduction in coronary heart disease associated with higher selenium levels (Table 1). Thirteen of 18 case control studies individually reached statistical significance. However, the three case control studies with at least 100 cases either failed to reach statistical significance, or only bare significance was achieved. Moreover, most case control studies did not make any adjustment for confounding factors, and only six of 18 made any adjustments.

Randomised trials generally used 100 µg selenium supplementation daily from yeast. The four larger studies were of high quality and had a long duration, of three to eight

Table 1: Relative risk of clinical coronary heart disease and selenium levels in tissue in observational studies, or supplementation in RCTs

Type of study	Number of studies (cases)	Relative risk (95% CI)
Cohort	14 (1,835)	0.85 (0.74 to 0.99)
Case control	16 (1,854)	0.43 (0.29 to 0.66)
RCTs	6 (452)	0.89 (0.68 to 1.2)

Table 1: Results for clinical coronary heart disease in randomised trials of selenium supplementation



years. Some had selenium combined with other vitamins or minerals. The results (Figure 1, Table 1) were not statistically significant.

Comment

There are some interesting lessons here, particularly the difference between case control studies that generally made no adjustments for confounding, and cohort studies that did. Of course, adjustment may not be the issue, but it is notable that both larger case control studies, and those that made adjustments for confounding factors had similar magnitude of effect as did cohort studies and randomised trials. Another, recent, randomised trial [2] found no effect of selenium supplementation on heart disease over 7.6 years of therapy.

This emphasises the fact that we have to look carefully at small observational studies, and not be overwhelmed by the size of an effect that could be just an artefact of how a study has been performed.

So what of selenium supplementation? We can probably be sure that this is no magic bullet to protect us against heart disease, especially if we have a varied and full diet. If there is an effect, it is small, probably no more than about 10%. That, of course, depends on one's point of view, and one persons 10% trivia could be someone else's 10% Grand Canyon. Selenium may be a bigger deal in other contexts.

Reference:

- 1 G Flores-Mateo et al. Selenium and coronary heart disease: a meta-analysis. American Journal of Clinical Nutrition 2006 84: 762-773.
- 2 S Stranges et al. Effect of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. American Journal of Epidemiology 2006 163: 694-699.

HEALTHY SURVIVAL

Suppose for a moment you are a man (Bandolier readers who are not will excuse us for a moment for a little reverie). Suppose you are 55 years old and healthy. Suppose you have developed a burning desire to:

- A Make sure that you get the very last drop out of your pension fund, or
- B To see Macclesfield win the European Championship (any other extremely remote sporting achievement), or
- C Want to see documents about the present government released under the 30-year rule.

Whichever you choose, you need to live for another 30 years, and since you are going to do that, you need to remain free of physical or mental problems. This has also been called exceptional survival, exceptional because so few actually achieve it. Bandolier 78 examined findings of the US Nurses' Study that showed that women with healthy lifestyles lived far longer than those who did not. We now have a similar finding for men [1].

Study

This was a report of the Honolulu Heart Program, which recruited over Japanese-American men in 1965-1968. The men were aged 45 to 68 years old (average 54 years). In subsequent years it has followed up mortality and development of major physical illness and cognition, during eight follow up visits up to 2005. A physical examination was performed at baseline, as well as biochemical and other variables.

Participants were classified into one of four types:

- 1 Non survivors, who died before a specified age (75, 80, 85, 90 years).
- 2 Usual survivors but disabled with a physical or cognitive disability.
- 3 Usual survivors with chronic disease but no disability.
- 4 Exceptional survivors who survived to a specified age without major chronic disease or cognitive or physical impairment.

Chronic disease of interest included coronary heart disease, stroke, cancer, COPD, Parkinson's disease, and diabetes. Physical impairment was defined as difficulty walking half a mile (about 800 metres).

Figure 1: Percentage of men in the cohort with different outcomes by age 85 years

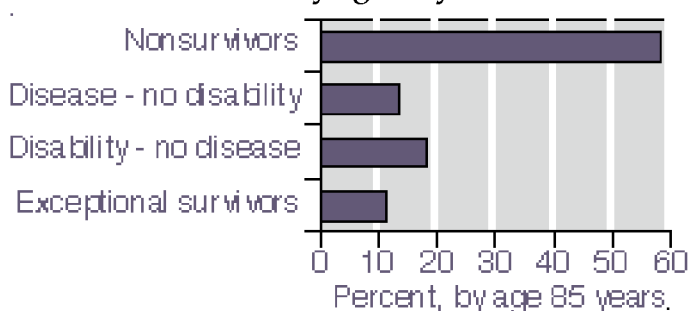


Figure 2: Probability of 55 yr man being alive at 75, 80, or 85 years, with 0 or ≥ 6 risk factors

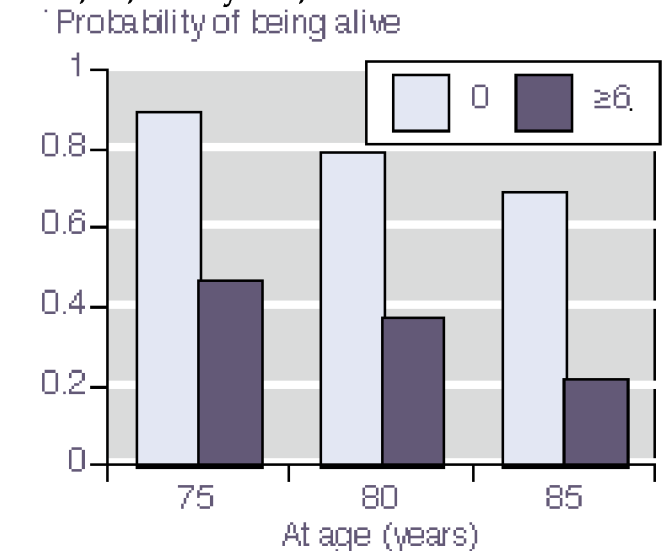


Figure 3: Probability of 55 yr man being free of serious disease at 75, 80, or 85 years if alive, with 0 or ≥ 6 risk factors

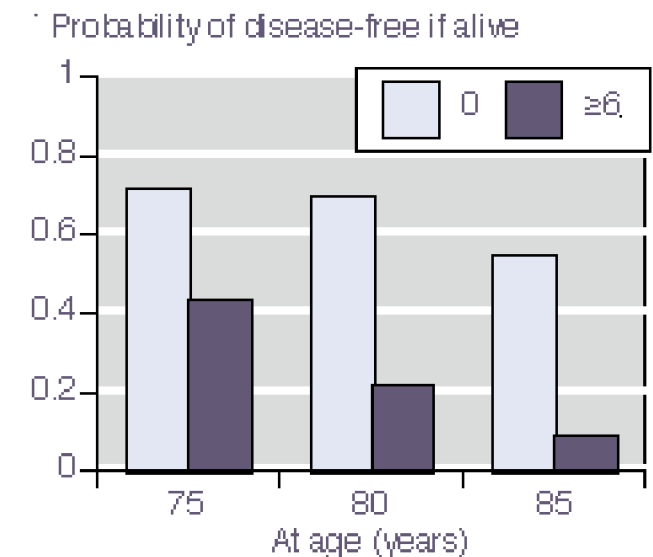
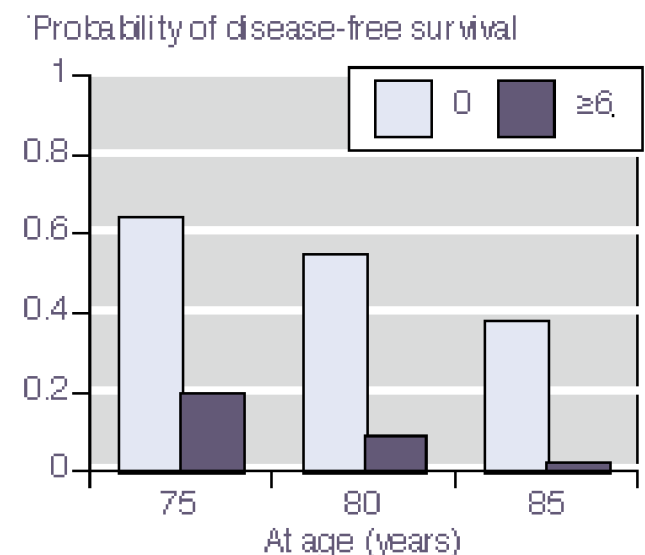


Figure 2: Probability of 55 yr man being alive at 75, 80, or 85 years and free of serious disease, with 0 or ≥ 6 risk factors



Results

Of 8006 original participants, 5,820 were healthy at baseline, did not die within one year, and had full baseline information including physical functioning. The classification at age 85 years is shown in Figure 1. Only 11% of men were exceptional survivors.

A set of risk factors was created after analysis of 29 different variables at baseline:

- Hyperglycaemia
- Hypertension
- High alcohol consumption (more than three drinks a day)
- Low education
- Overweight
- High triglyceride level
- Low grip strength
- Unmarried

In the absence of any of these risk factors, a man aged 55 would have a high probability of survival to age 85 years (69%), and of exceptional survival among those alive at 85 years free of disease and cognitive impairment (55%); the probability of being alive at a age 85 and being free of major disease was the product of these (38%). With six or more risk factors, there was much less likelihood of any of these outcomes (22%, 9%, and 2% respectively).

Figures 2, 3, and 4 show the results graphically. With between 1 and 5 risk factors, the probabilities gradually declined, in a more or less linear manner. Thus for a man aged 55 years with three risk factors, the chance of survival to 85 years would be 50%, of being an exceptional survivor if alive at 85 years 30%, and of being both alive and free of major disease at 85 years about 15%.

Comment

The major benefits of healthy living for men in this study were not dissimilar to those for women in the US Nurses’ Study (Bandolier 78). In the end it all comes down to the usual healthy living advice. Don’t smoke, drink moderately, don’t be overweight, exercise, eat sensibly, and, for men, get married (helps with all the above).

Most of all, there is a steep relationship between both survival and being free of major disease and the number of risk factors. In the range 0-2 risk factors, the decline is moderate. At three or more risk factors, the decline is steep with each additional one. The lesson is to keep them to a minimum.

Essentially this is the Bandolier healthy living advice, available from the website. So, if you want to know the winner of the 2035 FA Cup, Ashes, or World Series, you know how to do it.

Reference:

1 BJ Willcox et al. Midlife risk factors and healthy survival in men. JAMA 2006 296: 2343-2350.

ANTIBIOTICS FOR
ACUTE OTITIS EXTERNA

Acute otitis externa is an inflammation of the external ear canal, commonly known as swimmer’s ear. It can be treated with systemic or topical antibiotics, and topical treatment can involve several different types of antibiotic or antiseptic, sometimes combined with corticosteroid. A systematic review reveals just how little we know about what works best [1].

Systematic review

Searching involved using different databases for studies in any language. Articles were limited to acute otitis externa, parallel group design, and comparing antimicrobial and placebo, antiseptic and antimicrobial, and steroid plus antimicrobial versus antimicrobial alone or steroid alone. Outcomes used included clinical cure (absence of all signs and symptoms) or improvement (partial or complete relief). Different end points over 3 to 21 days were examined, with the intention to combine the final results.

Results

Twenty trials described as randomised were found, 18 with the required information for data pooling. The median size was 79 patients (range 28 to 842), all but one including children and adults. Half did not explicitly define acute otitis externa, and only half were defined as double blind.

Using the Oxford quality scoring system for randomisation, blinding, and withdrawal description, only 10 scored 3 out of 5 points, associated with a relative lack of bias. Those that were adequate (3, 4, or 5 out of 5) did not improve with time (Table 1).

There were 13 meta-analyses of these 18 trials, without sensitivity analysis according to quality score. The effect of topical antibiotic (neomycin) plus corticosteroid compared with placebo was described in only two good quality studies, with only 89 patients. Cure rates were much higher for antibiotic plus steroid than with placebo at 3-10 days. The NNT calculated for these two trials was 2.2 (1.6 to 3.7).

The only other comparisons of at least two treatments with relatively unbiased trials was for antiseptic versus antibiotic in three trials, with identical cure rates of about 60% at 7-10 days and 80% at 14 to 28 days.

Table 1: Trial quality over five decades

Decade	Quality score (range 1-5)	
	1 or 2	3-5
1960s	0	1
1970s	1	3
1980s	1	1
1990s	4	2
2000s	4	3

Comment

Another example where we have a paucity of data to guide therapy for a relatively common condition. Most trials were performed since 1990, yet most had poor quality scores indicating at best poor reporting quality, and at worse inadequate conduct. If anything, the quality of more recent trials was worse than those published earlier (Table 1). These are simple trials, and the influence of quality is well known. How can it be that trials of inadequate quality continue to be performed or reported? This shows a clear failure by ethics committees and journals, and a disservice to patients and professionals.

Reference:

- 1 RM Rosenfeld et al. Systematic review of topical antimicrobial therapy for acute otitis externa. *Otolaryngology – Head and Neck Surgery* 2006 134:S24-S48.

ANTIBIOTICS FOR ACUTE OTITIS MEDIA

The Achilles' heel of pooled analysis is that we concentrate on averages. No individual is average, and we could do with much less concentration on whether interventions work on average, but which patient characteristics determine where the intervention works best. No does it work, but in whom does it work? How can this be done? The answer is individual patient meta-analysis. Theoretically this can provide really useful information. Such an analysis for acute otitis media in children [1] holds out little indication that antibiotics are useful in any children.

Review

Investigators of trials were approached for individual patient data if their trials randomised children aged 0-12 years with acute otitis media, compared antibiotics with no treatment or placebo, and had pain and fever as an outcome. Of 10 such trials, six provided data.

Outcomes calculated were presence of pain (yes/no), fever (greater or less than 38°C), or both at 3-7 days. A series of pre-defined subgroup analyses were planned, together with logistic analysis to identify important correlates of treatment efficacy.

Table 1: Results of sub group analyses for antibiotics vs placebo in AOM

Subgroup	Number in analysis	Extended course of acute otitis media (%)		Relative risk (95% CI)	NNT (95% CI)
		Antibiotic	Placebo		
Overall result	1663			0.83 (0.78 to 0.89)	8 (6 to 11)
<2 years with bilateral AOM	273	30	55	0.64 (0.62 to 0.80)	4 (3 to 7)
<2 years with unilateral AOM	261	35	40	0.92 (0.76 to 1.1)	not calculated
Otorrhoea present (any age)	116	24	60	0.52 (0.37 to 0.73)	3 (2 to 5)
Otorrhoea absent (any age)	439	28	42	0.80 (0.70 to 0.92)	8 (4 to 20)

Outcome was pain, fever, or both at 3-7 days

EDITORS

Andrew Moore Henry McQuay
Pain Relief Unit
The Churchill, Oxford OX3 7LJ
Editorial office: 01865 226132
Editorial fax: 01865 226978
Email: andrew.moore@pru.ox.ac.uk
Internet: www.ebandolier.com
ISSN 1353-9906

Results

The six trials essentially tested amoxicillin versus delayed treatment or placebo. These six trials randomised 1,633 children. Overall, antibiotics reduced the incidence of an extended course of acute otitis media at 3-7 days by 13%, with an NNT of 8 (95% confidence interval 6-11).

Table 1 shows the overall result in more detail, together with those subgroups where there was a lower (better) NNT. The analyses indicated that the effect of antibiotics was modified by age, bilateral disease, and otorrhoea.

Comment

The authors of this analysis go to great pains to describe possible limitations, despite their individual patient analysis, and the great care they have taken in a detailed and sophisticated analysis. The take-home message, though, is that antibiotics seem to be most beneficial in younger children with bilateral acute otitis media, and where there is otorrhoea.

How much weight should we place on this? Not much, because differences between antibiotics and placebo disappeared by five or six days, numbers were small, and what differences there were came from differences with placebo (look at Table 1 carefully). This analysis nails down that there is no subgroup of children for whom antibiotics can be really useful in acute otitis media, unless there are complications or other consideration. It proves the utility of individual patient analysis.

Reference:

- 1 MM Rovers et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006 368:1429-1435.